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Cigarette smoking and male lung cancer in an area of very high incidence

I Report of a case-control study in the West of Scotland

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SUMMARY Altogether 656 male lung cancer cases and 1312 age and sex matched controls were interviewed between 1976 and 1981 in a case-control study of cigarette smoking habits and lung cancer in Glasgow and the West of Scotland, an area with the highest recorded incidence in the world. The relative risk of lung cancer increased significantly for smokers whose consumption was below 20 cigarettes per day but did not rise significantly in those who smoked more than 20 cigarettes per day. Other smoking characteristics such as inhalation and tar yields of brands smoked did not explain this finding. Additionally, the relative risks observed at all levels of cigarette consumption were low in comparison with those in the published literature. By constructing an index of cigarette exposure which included the tar yields of brands smoked, an assessment of the risk of lung cancer in relation to tar exposure independent of amount smoked was derived. Only in smokers of less than 15 cigarettes per day was there a statistically significant reduction in risk of lung cancer associated with lower levels of tar yield.

It is now more than 30 years since the publication of the first definitive epidemiological study by Doll and Bradford Hill on the aetiology of lung cancer in the United Kingdom.[1] None of the geographical areas in which these studies have been undertaken have as high an incidence of lung cancer as the West of Scotland.[2] In 1984, smoking-related cancers were responsible for 54% of all new male cancer cases in the Greater Glasgow Health Board area, and the male lung cancer mortality rate for the area was 158 per 100 000.[3]

This report of a case-control study of cigarette smoking and lung cancer is presented firstly because the relative risk above an average of 20 cigarettes per day does not rise significantly, contrasting with the majority of retrospective case-control studies published since Doll and Hill's original article,[1] and, secondly, because the results are supported by a prospective cohort study carried out at approximately the same period of time, between 1972 and 1984, in an adjacent geographical area which is demographically similar and has a similar male lung cancer mortality rate (156 per 100 000).[3]

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Material and methods

A total of 3125 patients admitted to general and respiratory wards in hospitals within urban West of Scotland were interviewed between January 1977 and May 1981. Potential cases and controls were chosen on the basis of the provisional diagnosis stated on admissions lists. The status as either case or control was subsequently confirmed by checking the final diagnosis for each admission in the Medical Records Department of the hospitals concerned and ultimately in the West of Scotland Cancer Registry.

Any interview with a presumptive diagnosis of lung cancer not subsequently confirmed in the Cancer Registry was discarded. Two controls were matched to each case, matching being made on the basis of age (within five years at the time of diagnosis), sex, and date and place of interview. Matching was made after the final diagnosis of each case and control had been established. The final data presented relate to a total of 656 cases of male lung cancer and 1312 age and sex matched controls.

Histological confirmation was obtained for 77% of lung cancer cases and cytological confirmation for

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18%. The remaining 5% of the lung cancer cases were diagnosed on clinical grounds.

Patients with no major tobacco-related disease as the diagnosis responsible for their current admission were accepted as controls. The major control diagnoses were acute infectious diseases, fractures, and cancers of the colon, rectum, stomach, and prostate and neoplasms of the lymphatic and haematopoetic tissue. No one disease group exceeded 10% of the total number of controls. Both case and control patients were interviewed in hospital by one of two specially trained interviewers. Arrangements were made to ensure, as far as possible, that the interviewers had no knowledge of the diagnosis from members of staff nor access to the case record. A standard questionnaire[4] was used to record and investigate the nature of present and past cigarette use, with particular emphasis on recording changes in the number of cigarettes, smoked, years of usage, and changes in brands during the smoker's lifetime, so as to provide the best possible estimate of exposure during lifetime up to the time of interview.

The age and social class distribution of cases and controls is given in table 1.

The most commonly used statistic in the literature to describe exposure to cigarette tobacco products is the average number of cigarettes smoked per day, and the most frequently used expression of risk, in terms of disease, is the relative risk. Average number of cigarettes per day has been based on the total amount smoked throughout the smoking lifetime. Relative risk has been estimated taking the matching of controls to cases into account.[5]

The questionnaire permitted further measures of cigarette exposure to be described, namely:

1 an estimate of the total number of cigarettes smoked until diagnosis (lifetime packets). This allowed for changes in the number of cigarettes smoked and any periods of stopping smoking to be taken into account.

2 an estimate of the total tar yield to which an individual had been exposed during his smoking lifetime.

Tar yields for the period before 1961 are not known routinely[6] and have been set at the 1961 level. Routine information on the tar yield of cigarettes between 1961 and 1970 is available only from the manufacturers. Since 1971, both the cigarette manufacturers and the Government Chemist have reported tar yields at regular intervals.[7] Using these data, an average tar yield was derived for each brand for each five-year time period, pre–1961, 1961–65, 1966–70, 1971–75, 1976–80. By considering the average number of cigarettes smoked by an individual on a brand basis for each of these intervals, a total tar yield index was constructed.

Thus, reductions in the tar yield of specific brands which have taken place since 1960 and changes between brands of different tar yields have been allowed for.

Ex-smokers have been defined as those who have given up smoking for at least one year. Pipe and cigar only smokers have been excluded from the results. The percentage of cases and controls currently smoking pipes and cigars in addition to cigarettes was 10% and 11% respectively.

Results

The relative risk of lung cancer for current smokers of increasing amounts of cigarettes smoked daily is shown in table 2. The relative risk shows a steep linear increase up to 7·6 for an average cigarette consumption of 15–24 cigarettes per day. Cigarette consumption above this level is associated with only a

Table 1 *Age and social class distribution of cases and controls.*

Age group (years)	*Cases*		*Controls*	
	No	*%*	*No*	*%*
<45	18	2·7	56	4·8
45 –	129	19·7	291	22·2
55 –	264	40·2	472	36·0
65 –	218	33·2	421	32·1
75 +	27	4·1	72	5·5
Total	656		1312	
Median age	60·5		61·2	
Social class*				
I	5	0·8	47	3·6
II	72	11·3	119	9·2
III	315	49·5	567	43·8
IV	103	16·2	309	23·9
V	142	22·3	252	19·5

*19 cases and 18 controls could not be classified.

Table 2 *Average number of cigarettes smoked daily by cases and controls and associated relative risk (ex-smokers excluded).*

Average number of cigarettes smoked daily (present smokers only)	*No of cases*	*No of controls*	*Relative risk*	*95% Confidence interval*
Never smoked*	13	145	1	
1–14	82	205	4·5	2·5– 8·1
15–24	248	361	7·6	4·2–13·8
25–34	76	113	8·6	4·6–16·1
35–49	59	66	9·7	5·1–18·4
50 +	25	26	7·8	3·7–16·4
Total	503	916		

* Never smoked tobacco of any kind.

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small increase in relative risk to 9·7 and falls among those who reported smoking more than 50 cigarettes daily on average.

The dose-response relation, that is, the increase in relative risk with increase in cigarette consumption, for those cases histologically confirmed is shown in figure 1. The sharp rise in risk for those smoking up to 15–24 cigarettes daily is apparent for both squamous and oat cell tumours. Above this level the flattening of the dose-response curve occurs for those with squamous cell cancer and declines (but not statistically significantly) for oat cell cancers. A relatively weak relation for those with adenocarcinomatous tumours is also shown.

Table 3 compares the smoking habits of those cases whose cell type was not distinguished or where no histology was obtained with those where a cell type was distinguished. No statistically significant differences are seen in the percentage of smokers in each category. Thus both groups were amalgamated.

Relative risks for the average number of cigarettes smoked per day, the total number of cigarettes smoked, and the total tar yields are given in table 4. The linear increase in relative risk rises to 11·5 for total tar yield at an average consumption equivalent to 25–34 cigarettes per day and does not appear to rise above this level even if more cigarettes are smoked (see appendix).

Figure 2 shows the relative risk of lung cancer for smokers of 25 cigarettes and more, for those who

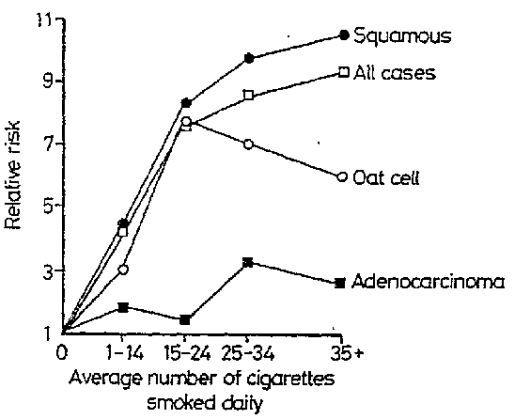

Fig 1 *Relative risk in relation to amount smoked for each cell type.*

Table 3 *Average number of cigarettes smoked daily in cases where the cell type was distinguished and in those where the cell type was not specified.*

Average number of cigarettes smoked daily (present smokers only)	Cell type specified		Cell type not specified	
	No	%	No	%
Never smoked*	12	3·1	1	0·9
1–14	63	15·9	19	17·8
15–24	193	48·7	55	51·4
25–34	61	15·4	15	14·0
35–49	47	11·9	12	11·2
50+	20	5·1	5	4·7
Total	396		107	

* Never smoked tobacco of any kind.

Table 4 *Relative risks for different measures of exposure.*

Level of exposure *	Measure of exposure: Average No cigs/day	Total lifetime packets	Total tar yield
Never smoked	1	1	1
1–14	4·5	3·8	3·7
15–24	7·6	7·0	7·0
25–34	8·6	10·6	11·5
35–49	9·7	12·1	10·5
50+	7·8	8·0	8·9

* See appendix.

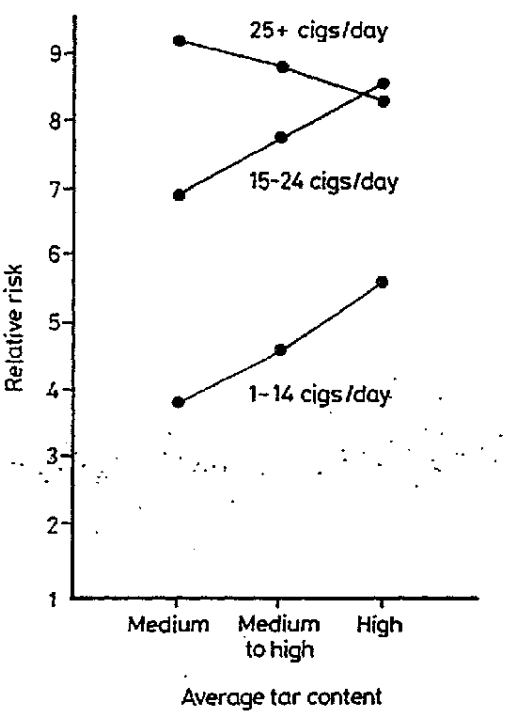

Fig 2 Relative risk in relation to average tar yield for light, medium, and heavy smokers.

smoked 15–24 ciga
smoked 1–14 ciga
exposure to medi
high (23–28 mg/ci
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Table 5 *Distributi
quantities for cases*

	Average tar yield
Low/Medium	
Medium	
Medium/High	
High	
Total cases	
Total controls	

* Percentage of cases sm
low/medium category.
** Percentage of controls
low/medium category.
Cases: χ^2_6 = 4·1, p = 0·6
Controls: χ^2_6 2·7, p = 0·8

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smoked 15–24 cigarettes per day, and for those who smoked 1–14 cigarettes per day in relation to their exposure to medium (17–22 mg/cigarette), medium/high (23–28 mg/cigarette), and high tar (>28 mg/cigarette) yield cigarettes. The relative risk did not change significantly (p=0·7) for smokers of 25 and more cigarettes per day regardless of the tar yield to which they were exposed. For smokers of 15–24 cigarettes per day, the relative risk fell as tar exposure decreased but this fall was not statistically significant (p=0·07). Smokers of 1–14 cigarettes per day also showed a decrease in relative risk with decreasing tar exposure. This reduction in relative risk was statistically significant (p=0·04).

Table 5 shows the average tar exposure in relation to the quantity of cigarettes smoked by the cases and controls. The percentage of those with high tar exposure among heavy smokers is similar in cases and controls.

Table 6 presents the reported inhalation of smokers in relation to the quantity of cigarettes smoked for both cases and controls. Smokers of less than 15 cigarettes per day seem less likely to be deep inhalers in contrast to the heavier smoking categories. Over 40% of smokers who smoked 25 or more cigarettes per day said they inhaled deeply.

Figure 3 shows the relative risk of lung cancer for the 140 cases and 350 controls who stopped smoking completely for periods ranging from one to 20 years relative to their average consumption before stopping. The pattern of declining risk with stopping smoking is similar for each group of smokers (the first point on fig 3 shows the relative risk of present smokers as in table 2). Only those who reported stopping smoking for at least five years or more show a decline in relative risk.

Table 5 *Distribution of tar yield for smokers of different quantities for cases and controls (present smokers only).*

Average tar yield	*Average No of cigarettes per day*				*Total*
	1–14	*15–24*	*25–34*	*34+*	
Low/Medium	0·0*	0·0	5·0	0·0	4
	1·0**	0·6	0·9	0·0	5
Medium	13·4	10·7	12·5	13·1	58
	15·6	17·9	14·2	12·1	123
Medium/High	80·5	85·2	76·2	83·3	405
	80·0	77·3	80·5	83·5	611
High	6·1	4·1	6·3	3·6	23
	3·4	4·1	4·0	4·4	31
Total cases	82	248	76	84	490
Total controls	205	361	113	92	771

* Percentage of cases smoking 1–14 daily whose average tar yield is in the low/medium category.

** Percentage of controls smoking 1–14 daily whose average tar yield is in the low/medium category.

Cases: χ^2_6 = 4·1, p = 0·65
Controls: χ^2_6 2·7, p = 0·85

Table 6 *Inhalation patterns for smokers of different quantities for cases and controls (present smokers only).*

Depth of inhalation	*Average No of cigarettes smoked daily*				
	1–14	*15–24*	*25–34*	*34+*	*Total*
Non-inhaler	9·5*	4·3	5·8	7·1	24
	9·8**	2·5	3·6	3·3	36
Slight	18·1	11·9	5·8	6·3	60
	19·1	14·0	5·4	3·3	98
Moderate	54·3	50·5	48·1	37·5	245
	52·0	48·9	48·2	45·1	376
Deep	18·1	33·3	40·4	49·1	156
	19·1	34·6	42·9	48·4	255
Total cases	82	248	76	84	490 (5 nk)
Total controls	205	361	113	92	771 (6 nk)

* Percentage of cases smoking 1–14 cigarettes daily who claim to be non-inhalers.

** Percentage of controls smoking 1–14 cigarettes daily who claim to be non-inhalers.

Cases: χ^2_9 = 34·0, p<0·001
Controls: χ^2_9 56·0, p<0·001

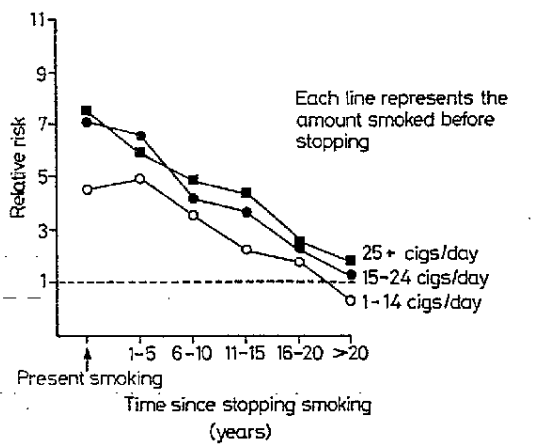

Fig 3 Relative risk in present smokers and ex-smokers according to time since stopping smoking and amount smoked before stopping.

Discussion

The major finding in this study is the steep increase in the relative risk of lung cancer observed in West of Scotland smokers with an average consumption of

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1–14 and 15–24 cigarettes daily, compared with the small increase in relative risk in smokers with a higher average daily consumption (table 2). This is at variance with the majority of the literature which describes a steady increase in relative risk above an average consumption of 20 cigarettes daily.

The validity of the findings in this study is supported by the following:

1 The procedures followed in this study are accepted as current practice in the design of case-control studies.[8] The median age of cases interviewed in the study was younger than in the West of Scotland generally. The control diagnoses were spread over a wide spectrum of non-smoking related diseases with no single control disease exceeding 10% of the total. Although a period of five years was allowed in matching the age at diagnosis of cases and controls, 82·5% fell within three years. The distribution of cell types was similar to that in previous studies although the rate of histological confirmation was somewhat lower.

2 The questionnaire used in this study has been used in many studies of smoking and disease over the past 30 years. Some 50 interviews were repeated by chance during the course of the study. Of these, 48 gave answers regarding cigarette consumption, which, when allocated to smoking exposure categories, were the same as previously given.

3 Variation between interviewers and the quality of the interviews conducted could be closely monitored throughout the study as only two interviewers were responsible for 95% of the interviews. Considerable care was also taken to ensure that they had no knowledge of the diagnosis.

4 The majority of the well known epidemiological associations of cigarette smoking and lung cancer can be reproduced using the data collected in this study; a decrease in relative risk in ex-smokers after five years since stopping[9] (fig 3); squamous and oat cell tumours associated with the highest levels of relative risk whereas adenocarcinomas showing only a minor association with cigarette smoking[10 11] (fig 1); a significant positive association between depth of inhalation and average daily consumption of cigarettes.[12]

The results of this study raise three main questions. Firstly, is the small increase in relative risk in smokers with a high average consumption due to under-reporting of cigarette smoking practice? Secondly, are the cigarette smoking habits of cases and controls different in terms of the type of cigarettes smoked and inhalation, particularly at the higher levels of cigarette consumption? Thirdly, is the proportion of lung cancer patients who are non-smokers different from that in other studies?

With increasing public awareness of the harmful effects of cigarette smoking, individuals, and cases particularly, may have under-reported their level of cigarette consumption, especially those at higher levels. However, in this study the proportion of heavy smokers among the cases (ie, the proportion of individuals who smoke more than 25 cigarettes per day) is larger than in most quoted case-control studies which have resulted in steadily increasing relative risks with increasing dose. The proportion of heavy smokers among the controls in this case-control study not surprisingly also exceeds that in the apparently healthy West of Scotland population sampled in the same period of time.[13] These factors both suggest that under-reporting of cigarette consumption is not a serious bias in this study.

The flattening of the dose-response relation could also have been explained if, among heavy smokers, cases were smoking lower tar cigarettes or inhaling less than controls. However, table 5 shows remarkable similarity between the tar exposure of cases and controls in each category of cigarette smoking with no significant differences detected, and table 6 shows no differences in inhalation between cases and controls.

The possibility also exists that average number of cigarettes per day does not provide an adequate estimation of total dose although this has often been used in the literature. Total lifetime packets, which incorporates the number of years of smoking, and total tar yield also produce a flattening of the dose-response relation at the higher levels of exposure.

Total tar yield is probably the best measure of exposure statistically. There was no increase in relative risk for smokers of 25 cigarettes per day and above whether they smoked high, medium/high or medium tar cigarettes. An increase in relative risk was present for smokers of 15–24 cigarettes per day for increasing levels of tar exposure but the increase in risk was not statistically significant. Only those who smoked 1–14 cigarettes per day showed a statistically significant reduction in relative risk as tar exposure declined from high to medium.

Thus, in an area of exceptionally high lung cancer incidence, there is a lack of increase of the relative risk of lung cancer at higher levels of cigarette smoking. We have been unable to explain this observation on the basis of confounding bias or artefact.

The low level of relative risk found at all levels of cigarette consumption coupled with the small increase in relative risk observed at the highest levels of smoking represent a paradox for an area with such a very high rate of lung cancer.

The existence of a higher than average proportion of heavy smokers in the West of Scotland population would not seem therefore sufficient by itself to be responsible for the high lung cancer rate. Thus the question of additional susceptibility to lung cancer in

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the local population is raised.

The finding of case-control studies are considerably enhanced if supported by prospective cohort studies. The accompanying paper[13] attempts to place the findings of this study in the context of a prospective cohort study of 7055 West of Scotland men with known smoking habits followed for 10½ years.

The data collection phase of this study was undertaken with the financial support of and under contract to the National Cancer Institute, Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, USA, as part of their Smoking and Health Program. Contract No. NO1-CP-05646.

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Statistical appendix

The validity of the indices of exposure to tobacco used in this paper has been examined by considering the contribution each makes to the statistical model of the dose-response relation. This is measured by the 'goodness-of-fit' statistic. If the use of past quantity smoked and historical tar data had been so unreliable as to be meaningless, increased random variation would have been introduced into the indices and no statistically significant improvement in 'goodness-of-fit' would have been apparent. As it was, the index 'lifetime packets' produced a better fit to the model of the dose-response relation than 'average number of cigarettes per day'. However, the best fit was achieved using the index 'total tar yield'.

Index	*Goodness of fit*	*Improvement in fit* (χ^2)*	*p value*
Null	1447		
Average number of cigarettes/day	1337		
Lifetime packets	1317	13·8	<0·001
Total tar yield	1306	18·1	<0·005

* Improvement in fit is expressed relative to the model using average number of cigarettes/day as the measure of exposure.

In order to compare the way in which the relative risk for each measure of exposure changes as the level of exposure increases, it is necessary to define a standardised scale for level of exposure (in the same manner as standard age groups are defined for the 'world standard' population). This has been achieved by defining boundaries in such a way that *an equal proportion of controls* is contained within a category for each measure of exposure. The choice of boundaries has been set to match those used for 'average number of cigarettes per day', this being a scale which is easily conceptualised and which appears most frequently in the literature.

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